

The University of Chicago

THE REDUCTION OF *dl*-ERYTHRONIC LACTONE
TO *dl*-ERYTHROSE

A PART OF A DISSERTATION SUBMITTED TO
THE FACULTY OF THE DIVISION OF THE
PHYSICAL SCIENCES IN CANDIDACY FOR THE
DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

~~1934~~
1938

By
BERTRAM DELAFIELD KRIBBEN

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[Reprinted from the Journal of the American Chemical Society, 61, 1720 (1939).]

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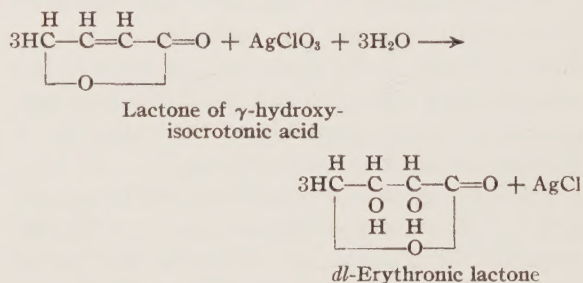


The Reduction of *dl*-Erythronic Lactone to *dl*-Erythrose¹

For some years past, work on the preparation and study of the eleven C₄-saccharinic acids has been carried on in these Laboratories.² The work, which is now completed, was done in order to provide data on the constants and properties of these acids that might be useful in detecting them in, and separating them from, reaction mixtures produced by the action of alkalis on the tetroses.

The next step in the program is the synthesis of the *dl*-tetroses themselves. A source of one of these tetroses, *dl*-erythrose, has been found in *dl*-erythronic lactone which is prepared by the oxidation of the lactone of γ -hydroxy-isocrotonic acid, obtained as a by-product in the synthesis of one of the C₄-saccharinic acids.³ The oxidation

is achieved with osmium tetroxide-activated silver chlorate⁴ according to the equation



Some success has been attained in the conversion of the *dl*-erythronic lactone so obtained into *dl*-erythrose. This paper gives an account of the work.

The optically active forms of the aldotetroses seem to be fairly well known, the constants of the threoses⁵ resting, perhaps, on a somewhat firmer

(1) This article is condensed from a dissertation presented by B. D. Kribben in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Chicago.

(2) Glattfeld and co-workers, *J. Am. Chem. Soc.*, **42**, 2314 (1920); **43**, 2675 (1921); **47**, 1742 (1925); **49**, 2309 (1927); **53**, 3164 (1931); **55**, 1114 (1933); **55**, 3663 (1933); **60**, 415 (1938).

(3) Glattfeld, Leavell, Spieth and Hutton, *ibid.*, **53**, 3164 (1931).

(4) (a) Hilmeyer Cohen, Ph.D. dissertation, University of Chicago, 1928; (b) Géza Braun, *J. Am. Chem. Soc.*, **51**, 235 (1929).

(5) Hockett, Deulofeu, Sedoff and Mendive, *ibid.*, **60**, 278 (1938).

basis than those of the erythroses.⁶ As far as the authors are aware there is found in the literature only one report of the isolation of these sugars in the racemic form.^{6a}

Two previous attempts to reduce *dl*-erythronic lactone to *dl*-erythrose in this Laboratory proved to be unsuccessful. Hutton⁷ tried sodium and other amalgams and reported a maximum yield of 2.5% of the aldehyde. Miss Stack⁸ attempted the reduction of both the lactone and the butyl ester, with hydrogen in the presence of platinum black. At both high and low pressures she obtained 60–70% yields of erythritol and found no evidence of aldehyde formation. These results indicate: (a) the rate of reduction of the aldehyde to erythritol is so much faster than the rate of formation of the aldehyde, that the concentration of the latter in the mixture is always very small; or (b) that, under the conditions of the experiment, the formation of the aldehyde is not a step in the mechanism by which the alcohol is formed. The former assumption seems the more probable in view of the high reactivity of the furanose type of aldose in general.

A more circuitous method of reducing sugar acids to aldehydes has been reported recently by Cook and Major.⁹ They prepared pentaacetylgluconic acid, converted it to the acid chloride and successfully reduced the latter to pentaacetylglucose by means of hydrogen in the presence of palladinized barium sulfate according to the procedure of Rosenmund.¹⁰ The yield was almost quantitative. Mochel¹¹ and Straitiff¹² have recently applied this procedure to the reduction of two of the C₄-saccharinic acids to the corresponding aldehydes and the method showed promise of being adaptable to the reduction of *dl*-erythronic lactone to *dl*-erythrose.

The first step to be accomplished was the preparation of *dl*-triacetyl-erythronic acid. Nef¹³ had prepared the diacetyl and dibenzoyl derivatives of *dl*-erythronic lactone, the former as a sirup and the latter as a crystalline solid. During the course of the work herewith reported, the diacetyl lactone was obtained in almost quantitative

yield as a crystalline solid which melted at 52.0–52.5°. It was hoped that, by the use of catalysts or higher temperatures, the lactone bond could be opened during acetylation and the triacetyl acid obtained. The use of acetic anhydride with pyridine, zinc chloride and hydrochloric acid as catalysts in the acetylation procedures did not bring this about. This failure showed that it would be necessary to break the bond previous to acetylation attempts, if the triacetyl acid was to be obtained. The simplest method for breaking the lactone bond proved to be conversion to a salt.

The calcium salt was prepared according to the method of Snoddy¹⁴ but attempts to acetylate it proved unsuccessful. The sodium and potassium salts were then prepared. Attempts to crystallize these salts from water were unsuccessful. However, when the lactone was dissolved in absolute methyl alcohol and the solution treated with alcoholic alkali at low temperatures, white crystalline products were obtained. The sodium salt was very hygroscopic; the potassium salt much less so.

The sodium salt reacted with acetylating agents with great violence but the potassium salt was acetylated smoothly at low temperatures by means of acetyl chloride. Potassium chloride precipitated during the reaction with the potassium salt. After removal of this salt and the excess acetyl chloride, followed by concentration of the solution, there remained an almost colorless sirup that could neither be distilled without decomposition nor induced to crystallize. The neutralization equivalent of this sirup indicated that it was composed to a large extent of the triacetylated *dl*-erythronic acid. This conclusion was confirmed by the preparation and analysis of the calcium salt. The triacetylated acid, upon treatment with highly purified thionyl chloride, was converted into the acid chloride. It is interesting to note that some workers¹¹ have reported difficulties in the preparation of the acid chlorides by means of thionyl chloride and have, therefore, preferred phosphorus pentachloride as the chlorinating agent. These difficulties were encountered in this work, when a supposedly pure commercial grade of thionyl chloride was used. However, carefully purified thionyl chloride proved to be satisfactory.

The reduction of the triacetyl acid chloride was

(6) Felton and Freudenberg, *J. Am. Chem. Soc.*, **57**, 1637 (1935).

(6a) Ruff, *Ber.*, **34**, 1365 (1901).

(7) Donald Hutton, Ph.D. dissertation, University of Chicago, 1930.

(8) Glattfeld and Stack, *J. Am. Chem. Soc.*, **59**, 753 (1937).

(9) Cook and Major, *ibid.*, **58**, 2410 (1936).

(10) Rosenmund, *Ber.*, **51**, 585 (1918).

(11) Glattfeld and Mochel, *J. Am. Chem. Soc.*, **60**, 1011 (1938).

(12) Glattfeld and Straitiff, *ibid.*, **60**, 1384 (1938).

(13) Nef, *Ann.*, **357**, 250 (1907).

(14) Snoddy, S.M. dissertation, University of Chicago, 1934.

carried out in a manner prescribed by Rosenmund.¹⁰ Hydrogen was bubbled into a xylene solution of the acid chloride in which was suspended palladinized barium sulfate. After a short induction period, the evolution of hydrogen chloride began, and the reaction proceeded smoothly until it was about 85% completed when the rate became extremely slow. The course of the reaction was followed by determination of the amount of volatile acid and chloride entrained by the excess hydrogen as it bubbled through the reaction mixture (see Experimental Part). Both the acid and chloride were determined because it was found that hydrogen chloride was not the only volatile acid produced and the true extent of the reduction could be ascertained only by the determination of the chloride content of the effluent gases. The results of these analyses are given in the table below.

TABLE I
REDUCTION OF THE ACID CHLORIDE

Time, min.	N NaOH consumed, cc.		Redn. calcd. from NaOH consumed, %	
	N AgNO ₃ consumed, cc.		AgNO ₃ consumed, %	
	Acid chloride		30.0 g.	
	Pd-BaSO ₄ catalyst		2.0 g.	
	Dry xylene		100.0 cc.	
5	0.83	..	0.77	..
8	1.66	..	1.55	..
10	2.50	..	2.32	..
14	4.99	..	4.65	..
19	8.31	..	7.72	..
24	12.5	..	11.6	..
43	24.9	21.9	23.2	20.4
60	37.4	32.2	35.9	29.3
79	49.9	43.0	46.5	40.2
102	62.4	54.0	58.1	50.4
118	70.6	61.4	66.0	57.2
147	83.1	72.5	77.5	67.5
172	91.5	..	85.5	..
187	95.8	..	89.1	..
204	100.0	87.5	93.7	81.5
231	104.0	90.8	96.8	84.3
275	108.2	93.0	100.7	87.5
Calcd.	107.2	107.2		

After removal of the catalyst and the xylene, the reaction mixture was fractionated at reduced pressure. The analysis of the main fraction which boiled at 126–129° at 2 mm. showed that reduction of the acid chloride to the aldehyde had been accomplished but that a diacetyl- instead of a triacetyl-erythrore had been produced. This unexpected result was verified by the preparation and analysis of the 2,4-dinitrophenylhydrazine derivative of the product. The compound produced was apparently the di-

nitrophenylhydrazone of neither triacetyl- nor diacetyl-erythrore. It contained 45.70% of carbon and 14.82% nitrogen instead of the 45.07% carbon and 13.15% nitrogen which are theoretical for the dinitrophenylhydrazone of triacetyl-erythrore and the 43.75% carbon and 14.58% nitrogen which are theoretical for the dinitrophenylhydrazone of diacetyl-erythrore. While these results are not close enough to either set of figures to prove the identity of the compound, they do indicate that one acetyl group was lost either in the reduction step or the subsequent fractionation. That this loss took place in the reduction step is indicated by the fact that acetaldehyde was present in the alkali solutions through which the hydrogen was passed after it left the reaction flask.

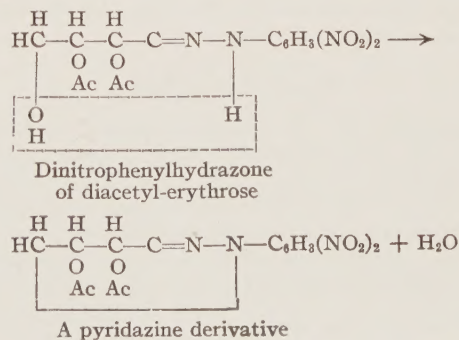
But the loss of one acetyl group and replacement by a hydrogen atom alone would not give a product of the correct composition for an analysis such as was obtained for this dinitrophenylhydrazine derivative. This change together with the loss of one molecule of water, however, would do so as the data in the following table show. The agreement in the nitrogen figure is not good but, because of the difficulties

THE DINITROPHENYLHYDRAZINE DERIVATIVE

	A		B	
	Triacetyl- dinitro- phenyl- hydrazone C ₁₆ H ₁₅ N ₄ O ₁₀	Diacetyl- dinitro- phenyl- hydrazone C ₁₄ H ₁₃ N ₄ O ₈	B-H ₂ O C ₁₄ H ₁₃ N ₄ O ₉	Found
C	45.07	43.75	45.90	45.70
H	4.22	4.17	3.83	3.62
N	13.15	14.58	15.30	14.82

inherent in nitrogen determinations by the combustion method in compounds of this type, the low figure obtained is perhaps not surprising.

The structure of the compound under discussion has not been determined. Mr. E. M. May of this Laboratory has suggested that the loss of a molecule of water might have occurred as indicated.



alkali had been added a gummy precipitate began to separate. The gum was triturated in the solution until it hardened to a cake. After about two hours the precipitation seemed to be complete. Most of the reaction solution was decanted, the cake was loosened from the sides of the dish and ground to a paste in the presence of a small amount of the solution. The paste was transferred to a Büchner funnel, the solid washed thoroughly with methyl alcohol, and dried in a vacuum desiccator: yield 132 g. of a stable white crystalline powder, 76% of the theoretical calculated as potassium erythronate.

Anal. Calcd. for $C_4H_7O_5K$: C, 27.56; H, 4.05; K, 22.45. Found: C, 27.76; H, 4.03; K, 22.47.

The Preparation of *dl*-Sodium Erythronate.—This salt was prepared in exactly the same manner as the potassium salt. The yield in the case of this salt was lower, about 60%. The product was a very hygroscopic white powder. Unless it was kept in a desiccator it soon turned into a greenish-brown sirup.

Anal. Calcd. for $C_4H_7O_5Na$: C, 30.38; H, 4.43; Na, 14.46. Found: C, 30.52; H, 4.48; Na, 14.37.

The Preparation of *dl*-Triacetyl-erythronic Acid (herein after called the triacetyl acid).—To 245 g. of freshly distilled acetyl chloride in a wide-mouthed Erlenmeyer flask was added, in small portions, 100 g. of potassium erythronate. Hydrogen chloride was evolved copiously and time was allowed between additions for the foam to subside. After all the potassium salt had been added and the evolution of hydrogen chloride had practically ceased, the flask was attached to a reflux condenser and the reaction mixture was heated on a boiling water-bath for one hour. At this point the mixture was a viscous sirup in which the potassium chloride was held in colloidal suspension. Addition to the sirup of six volumes of dry ether caused the coagulation and precipitation of the salt. The precipitate was removed by filtration and the filtrate treated with 2 g. of activated carbon. After removal of the carbon, the ether solution was evaporated at reduced pressure to a viscous, almost colorless sirup. The sirup was moderately soluble in water, quite soluble in ether and alcohol, and insoluble in chloroform, ligroin, and benzene. It did not crystallize from any of these solvents: yield 128 g., or 74%.

Anal. Calcd. for the triacetyl acid, $C_{10}H_{14}O_8$: neut. equiv., 65.5. Found: neut. equiv., 66.1.

Attempts to distil the sirup at 2 mm. resulted in rapid decomposition. A small fraction was recovered between 156–160° and later identified as the diacetyl lactone. Acetic anhydride was shown to be present in the distillate. Most of the material in the distilling flask was converted into a black tar.

The Preparation of *dl*-Calcium Triacetyl-erythronate.—Fifteen grams of the triacetyl acid dissolved in 40 cc. of 80% methyl alcohol was warmed to 40° and 2 g. of calcium carbonate added. After the evolution of carbon dioxide had ceased the solution was cooled, the precipitate was allowed to settle, and the supernatant liquid decanted. The precipitate was dried on a water-bath and thoroughly washed with ether to remove any unchanged acid. The precipitate was then treated with 50 cc. of water and the excess calcium carbonate removed by filtration. The calcium salt in the filtrate was again precipitated by the addi-

tion of 50 cc. of methyl alcohol. The precipitate was removed by filtration, washed with ether, and dried over phosphorus pentoxide; yield 6.3 g. or 37%. The product was a stable white powder moderately soluble in water.

Anal. Calcd. for calcium triacetyl-erythronate $C_{20}H_{26}O_{16}Ca$: C, 42.66; H, 4.62; Ca, 7.13. Found: C, 42.60; H, 4.66; Ca, 7.21.

The Preparation of *dl*-Triacetyl-erythronyl Chloride.—Twenty-five grams of the triacetyl acid and 25 g. of purified thionyl chloride (see below) were mixed and the mixture allowed to stand overnight in a flask fitted with a reflux condenser and protected from atmospheric moisture with a calcium chloride tube. The following day the mixture was refluxed on a water-bath until the evolution of hydrogen chloride had practically ceased (about four hours). Very cold water was circulated through the reflux condenser to prevent the loss of thionyl chloride. The residue was distilled at reduced pressure. The main fraction boiled between 115–130° at 2 mm. This fraction was again distilled at 2 mm. and from it there was obtained 21 g. of a mobile colorless liquid which boiled at 114–116°; a 79% yield calculated as triacetyl acid chloride. The substance fumed in moist air and possessed a sharp odor similar to that of hydrogen chloride.

Anal. Calcd. for the triacetyl acid chloride, $C_{10}H_{13}O_7Cl$: C, 42.77; H, 4.67; Cl, 12.64; neut. equiv., 55.9. Found: C, 42.77; H, 4.43; Cl, 12.77; neut. equiv., 56.1.

The Purification of Thionyl Chloride.^{16,17}—Two hundred grams of thionyl chloride was mixed with 30 g. of quinoline and distilled through a Schneider column. The fraction which boiled at 74–78° was mixed with 30 g. of boiled linseed oil and again distilled through the Schneider column. The fraction which boiled at 75–76° was colorless and remained so when kept in the dark. It was this fraction which was used in the preparation of the acid chloride.

The Reduction of *dl*-Triacetyl-erythronyl Chloride.—Thirty grams of the acid chloride was dissolved in 100 cc. of dry xylene and 2 g. of palladinized barium sulfate (5% Pd) catalyst added.¹⁸ The flask which contained the solution was attached to a reflux condenser and the mixture was heated to 135° in an oil-bath. Hydrogen, purified and dried by passage through 5% solutions of silver nitrate and potassium permanganate, then through concentrated sulfuric acid and copper gauze at dull red heat and finally through soda lime and phosphorus pentoxide, was introduced into the solution at such a rate as to keep the catalyst in uniform suspension. After a few minutes the evolution of hydrogen chloride began and proceeded smoothly, gradually lessening as the reaction approached completion. The effluent gases from the reflux condenser were conducted into a solution which contained a known amount of alkali and a few drops of phenolphthalein. When the alkali solution changed color, the effluent gases were conducted immediately into another solution of known alkali content. By noting the time at each color change and consequently the time required for the production of a known quantity of hydrogen chloride, both the rate and extent of the reduc-

(16) H. Meyer and R. Turnau, *Monatsh.*, **28**, 153 (1907).

(17) H. Meyer and K. Schlegel, *ibid.*, **34**, 569 (1913).

(18) Gattermann and Wieland, "Laboratory Methods of Organic Chemistry," 22d edition, The Macmillan Co., New York, N. Y., 1934, pp. 369–370.

tion of the acid chloride were followed (see Table I). The chloride in these solutions was estimated by titration with a normal solution of silver nitrate with dichlorofluorescein as the indicator. The chloride content of the solutions, calculated as hydrogen chloride, did not account for all of the acid present. Attempts were made to identify this additional volatile acid but they were unsuccessful. It was noticed that the solutions used for the estimation of the chloride had a distinct odor of acetaldehyde. This aldehyde probably was produced by the reduction of the acetyl group that was lost from the triacetyl acid chloride during the reduction process (see analysis below). When the chloride determination indicated that the reduction was 85% complete, the rate of reaction had become very slow and the reduction was discontinued in order to prevent thermal decomposition of the product obtained.

The xylene was removed by the introduction of the reaction solution dropwise into a small Claisen flask, evacuated to 10 mm. and heated to 100°. Attempts to distil the reaction mixture at reduced pressure in the ordinary manner caused so much foaming that serious mechanical loss resulted. The residue was fractionated at 2 mm. A small fraction which distilled between 114–120° proved to be unchanged acid chloride. The main fraction distilled between 125–140°. A second fractionation of this portion yielded 14.5 g. of a mobile, colorless liquid which boiled at 126–129° at 2 mm., a yield of 20% calculated as diacetyl-erythrose. The product possessed a mild aromatic odor and gave no test for chloride. It quickly reduced boiling Fehling's solution.

Anal. Calcd. for diacetyl-erythrose, $C_8H_{12}O_6$: C, 47.03; H, 5.92; neut. equiv., 102. Found: C, 47.20; H, 5.80; neut. equiv., 99.3.

The Reaction of *dl*-Diacetyl-erythrose with 2,4-Dinitrophenylhydrazine.—Two grams of the diacetyl-erythrose was dissolved in 50 cc. of a saturated solution of 2,4-dinitrophenylhydrazine in ethyl alcohol and the mixture was boiled for two minutes. Upon the addition of 5 drops of concentrated hydrochloric acid the solution immediately turned from orange to bright yellow. The solution was stored overnight in the icebox during which time a crop of bright yellow, needle-like crystals formed; yield 0.3 g. These were removed by filtration and recrystallized twice from a small quantity of methyl alcohol; m. p. 172–173°. Further recrystallization did not raise the melting point.

Anal. Calcd. for $C_{14}H_{14}N_4O_8$ (see above): C, 45.90; H, 3.83; N, 15.30. Found: C, 45.70; H, 3.62; N, 14.82.

The Hydrolysis of *dl*-Diacetyl-erythrose.—A mixture of 10 g. of the diacetyl-erythrose and 10 cc. of water was heated to 70° and held at that temperature until all the

aldehyde had dissolved. The solution was extracted with ten 10-cc. portions of chloroform to remove the acetic acid formed during the hydrolysis. It was then evaporated over phosphorus pentoxide in a vacuum desiccator to a light colored viscous sirup; yield 2.4 g. or 41%. The odor of acetic acid was still quite noticeable in the sirup but attempts to remove it by further extraction with chloroform were unsuccessful. The sirup readily reduced cold Fehling's solution.

Preparation of *dl*-Erythrose Phenyllosazone.—To a solution of 2 g. of the sirupy *dl*-erythrose in 3 cc. of 95% ethyl alcohol were added 2 g. of freshly-distilled phenylhydrazine and 2 g. of glacial acetic acid. The solution was allowed to stand in the dark for twelve hours. During this time a small quantity of brownish-yellow crystals had formed. They were separated by filtration and recrystallized from benzene; m. p. 162–165°.

Summary

1. *dl*-Diacetyl-erythronic lactone was prepared in almost quantitative yield by the acetylation of the lactone. It was a crystalline solid which melted at 52.5–53°. It has been reported heretofore only as a sirup.

2. The potassium and sodium salts of *dl*-erythronic acid as well as *dl*-triacetyl-erythronic acid and its calcium salt are reported for the first time.

3. Triacetyl-erythronic acid was converted into the corresponding acid chloride in high yield. This acid chloride was reduced according to the method of Rosenmund as modified by Cook and Major. Diacetyl-erythrose, instead of the expected triacetyl-erythrose, was obtained.

4. A crystalline product was obtained by the action of 2,4-dinitrophenylhydrazine upon the *dl*-diacetyl-erythrose. The analytical data showed that two molecules of water had been eliminated in the course of the reaction and the compound has been characterized tentatively as a pyridazine derivative.

5. *dl*-Diacetyl-erythrose was hydrolyzed to *dl*-erythrose, which was recovered as a light yellow sirup.

